Q & A

Tony Pawson

Tony Pawson got his Ph.D. in 1976 after working at the ICRF with Alan Smith. He did his postdoc in Berkeley, and then moved to the University of British Columbia in Vancouver to start his own lab. When he realized that it actually rains most of the time on the Canadian west coast, he moved to Toronto as a founding member of the Samuel Lunenfeld Research Institute of Mt. Sinai Hospital, where he has been ever since. During his Ph.D. he became interested in how overexpression of a single oncogenic protein could elicit profound changes in many different aspects of cellular behaviour; in looking for common features of signaling pathways he later stumbled on the SH2 domain. For the last 25 years he has been trying to understand how such pathways are organized, and what they do in cells and organisms.

What is your favourite paper? Martin, G.S. (1970). Rous sarcoma virus: a function required for the maintenance of the transformed state. Nature *227*, 1021–1023. Steven Martin isolated a mutant of Rous sarcoma virus (RSV) which was temperature-sensitive for its ability to induce malignant transformation of infected cells, but not for viral replication. This suggested that the entire cancerous phenotype of an RSV-infected cell could be attributed to a dedicated oncogene, later named v-Src. The temperature-sensitive phenotype was subsequently found to result from inactivation of the mutant v-Src tyrosine kinase at the non-permissive temperature. The implications of this finding were absolutely profound, and still boggle the mind some 30 years later. As a happy coincidence, I ran into Steve while at the ICRF, and was fortunate to work in his lab as a postdoc in Berkeley.

What turned you on to biology in the first place? I had an engaging and enthusiastic biology teacher in school who absolutely fascinated me with the idea that one could understand the biochemistry of cells and organisms, and so get an idea about how life worked. It was a heady thought, and I've been completely hooked ever since. Also, I was no good at any other job I tried. I've been very lucky in my mentors, and in the places that I ended up. Tim Hunt was one of my undergraduate tutors at Cambridge, and fired me up about doing experiments. He also told me that the most difficult part of science can be finding the right-sized bits of tubing to fit on columns. I had no idea what I was getting into when I went to ICRF for my Ph.D., as it had very few students at the time. It was a sink-or-swim environment, but an exceptionally exciting one, with work on oncogenic viruses revealing many of the key aspects of malignant transformation and molecular biology. In California I was exposed to the early days of cellular oncogenes, and upon moving to Vancouver, was fortunate to have Michael Smith as a neighbour, and so to have access to the technology of site-directed mutagenesis in its infancy. Perhaps my best stroke of good fortune was to work closely with people like Janet Rossant, Alan Bernstein and Joe Culotti in Toronto, who taught me about genetics and the relationship of signaling processes to development.

What are your current interests? Unfortunately I have too many. I am interested in several different aspects of cell biology, and don't have enough discrimination to focus (though I routinely advise everyone else to do so). One of my new enthusiasms is cell polarity, because it is so fundamental to the organization of cells and tissues. We're starting to learn about an interconnected series of protein complexes that control polarization, and related processes like asymmetric cell division, and it's going to be intriguing to know how they actually work. I'm also excited by the findings that pathogenic microorganisms and mutant cellular proteins can re-wire signaling pathways, in effect teaching the cell to do new things. Using the same logic, we should be able to experimentally — and perhaps therapeutically — re-wire cellular signaling to modify cellular behavior in pre-determined ways, and I'd love to see this happen. Now that we understand a lot about the bits and pieces through which signaling systems are put together, the challenge is to understand how they function in unison to induce complex cellular behaviour. Even more daunting is the question of how tissues and organs form. Hence the current vogue for systems biology.

What are the big challenges in your field? We've been arguing for at least 30 years that if we understood the molecular basis for malignant transformation, this would lead to new therapies for cancer. Drugs such as Gleevec, an inhibitor of the Abl and Kit kinases in chronic myelogenous leukemia and gastro-intestinal stromal tumours, respectively, are starting to validate this logic, but it is very early days for such new treatments. There is a tremendous challenge in translating our molecular data about cellular function into useful remedies for disease, while at the same time bearing in mind that our knowledge about how cells work is still very superficial.

What advice would you offer someone wondering whether to start a career in biology? Only do it if you're really passionate about it, and have an aptitude for it. If that's the case, don't hesitate. Follow your nose about what is interesting. Look for subjects where there are important questions that are not being addressed. Curiously, the more you know about a field, the more difficult it becomes to spot what's missing, so if you find yourself asking "how come no-one knows the answer to that?", you may have hit on a good project. Don't be afraid of making mistakes, as you will anyway; you can't learn to ride a bike without falling off.

What will be the impact of 'big biology'? There's a lot of unnecessary worry about 'big biology'. For the foreseeable future, I believe the most entertaining and productive aspect of biology will

remain figuring out the specifics of how particular cellular processes or machines actually work. Most biologists love this kind of scientific sleuthing. At the same time, there are great rewards to be had from taking basic ideas, and exploring them on a large scale, especially if we want to know how the whole cell (or tissue, or organism) is put together. I think there's a tendency to equate 'big' with mindless, which is far from the case. Large datasets and innovative techniques challenge us to think in new ways, which can't be bad. These broad experiments also force us to work cooperatively, which is something we're not very used to.

Any views on journals and publication? If your work is significant and worthwhile, people will find it regardless of where it's published, especially in this age of electronic browsing. Groundbreaking work may be hard to get into the 'top' journals, because it doesn't fit established norms; by the same token, if you publish something in a 'top' journal that's trendy but isn't really much good, it doesn't help you in the long run. The main question is whether a paper stands the test of time. There's a tendency on the part of students to view publication in anything other than the 'top' journals as a failure, and I think this is a huge mistake. It seems to me that electronic publishing is starting to level the playing field, and other web-based forms of publication are springing up, which is very healthy. I believe that peer review is important, but is currently overdone — it is not uncommon for a referee to see the same paper through three rounds of revision. This is a waste of time, and runs the risk that the authors end up publishing what the reviewers or editors want to see, rather than the paper the authors actually have in mind. The question is how to maintain a significant level of peer review, while making the options for publication as diverse as possible.

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Feature

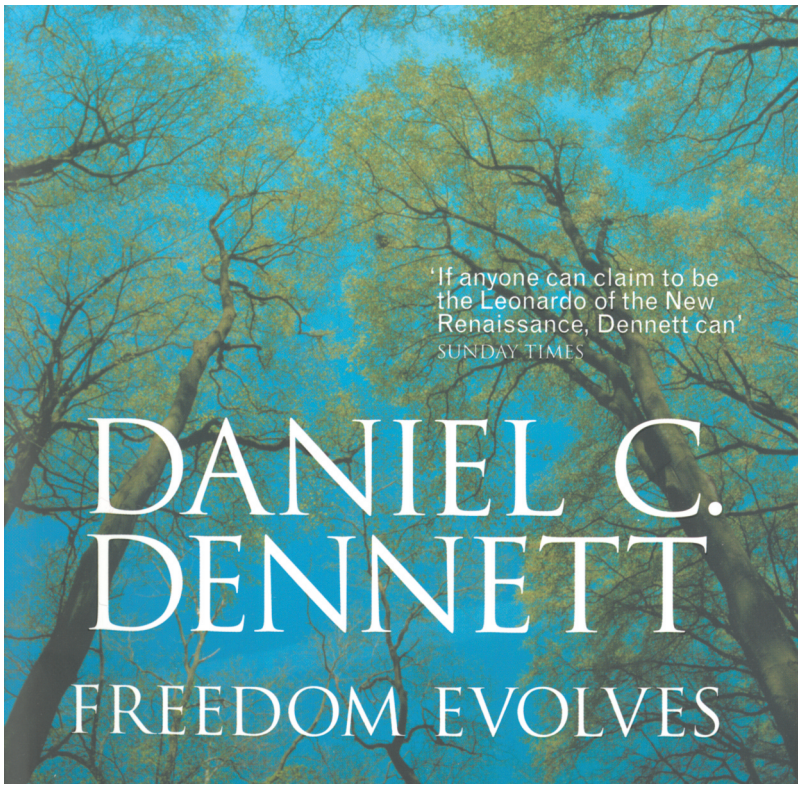
A biologist's thinking man

Philosopher Daniel Dennett believes he has an evolutionary explanation for one of biology's most difficult concepts: free will. **Nigel Williams** reports on his latest book.

The philosopher, Daniel Dennett, has been the doyen amongst his profession for many biologists with his series of popular books looking at questions thrown up by Darwin's work. How does natural selection lead to such things as consciousness and minds? In recent years his books on such issues have earned him the respect of a formidable list of academics. Philosopher Richard Rorty praised his 'extraordinarily lucid argumentation'. Steve Pinker credited his 'twinkling wit' and Richard Dawkins referred to his writing as a 'torrent of stimulating thought'.

But his unstinting materialism, which he now calls naturalism, has roused many critics of his approach. The question hangs around the issue of determinism. This is the issue of Dennett's new book. As he points out, educated people today are often trapped in a strange kind of double-think on the topic. Officially, they believe physical science calls for determinism, which proves they have no control over their lives. But in actual living, most of the time they do assume they have this control. They ignore their supposedly scientific beliefs but these can still cause deep underlying anxiety, confusion, guilt and a sense of futility.

"The proper job for philosophers here is to clarify and unify the often warring perspectives into a single vision of



Material gain: 'Philosophical investigations are not superior to, or prior to, investigations in the natural sciences.' Freedom Evolves by Daniel Dennett is published by Viking in the US ($24.95) and by Allen Lane in the UK (£20).